REMARKS

Claims 28-47 were pending in the present application. Claims 28, 37 and 44 have been amended. Claims 29, 34-35, 41-42 and 45-46 have been canceled. As such, claims 28, 30-33, 36-40, 43-44 and 47 are currently pending. The Examiner's rejections are as follows:

I. The Examiner has rejected claims 28, 31-33 and 36 under 35 USC §102(b) as allegedly being anticipated by Fonknechten et al., 1992, Hum. Genet. 88:508-512 (hereafter Fonknechten)

II. The Examiner has rejected claims 28, 31-33 and 36 under 35 USC §102(b) as allegedly being anticipated by Broude et al., 2001, Proc. Natl. Acad. Sci. 98:206-211 (hereafter Broude)

III. The Examiner has rejected claims 37-38 and 43 under 35 USC §102(b) as allegedly being anticipated by Shuber, US Patent No. 5,834,181

IV. The Examiner has rejected claims 28-47 under 35 USC §103(a) as allegedly being unpatentable over Hsu et al., 2001, Clin. Chem. 47:1373-1377 (hereafter Hsu) in view of the Cystic Fibrosis Mutation Database (hereafter CFMDB) and Fors et al., 2000, Pharma. 1:219-229 (hereafter Fors) and Hall et al., 2000, Proc. Natl. Acad. Sci. 97:8272-8277 (hereafter Hall)

I. The claims are novel over Fonknechten

The Examiner has rejected claims 28, 31-33 and 36 under 35 USC §102(b) as allegedly being anticipated by Fonknechten. In particular, the Examiner contends that Fonknechten teaches one-step PCR-cDNA amplification on extracted RNA from patient blood samples followed by analysis of the amplification production, with product analysis detection of a plurality of CFTR alleles using electrophoresis (Office Action, page 3). The Applicants disagree that Fonknechten anticipates claims 28, 31-33 and 36. However, to expedite the prosecution of the present application, while retaining the right to prosecute the original claims in the future, the Applicants have amended the claims to recite "…simultaneously amplifying ….. at least 20 CFTR alleles from said CFTR target nucleic acid wherein said at least 20 CFTR alleles comprise single nucleotide polymorphisms and deletion mutations ….to generate said at least 20 amplified

CFTR alleles…and exposing said at least 20 CFTR alleles to a plurality of detection assays wherein said detection assays comprise invasive cleavage assays ….” Support for the amendments is found in the specification at, for example, Example 9. Fonknechten does not teach simultaneous amplification of at least 20 CFTR alleles wherein said at least 20 CFTR alleles comprise single nucleotide polymorphisms and deletion mutations, or exposure to detection assays comprising invasive cleavage assays. As such Fonknechten does not anticipate the claims and the Applicants respectfully request that the Examiner withdraw the rejection.

II. The claims are novel over Broude

The Examiner has rejected claims 28, 31-33 and 36 under 35 USC §102(b) as allegedly being anticipated by Broude. In particular, the Examiner contends that Broude teaches low cycle number PCR suppression amplification of patient samples in a multiplex format, followed by gel electrophoresis (Office Action, pages 3-4). The Applicants respectfully disagree that Broude anticipates claims 28, 31-33 and 36. As stated above, the claims have been amended to recite simultaneous amplification of at least 20 CFTR alleles comprising SNPs and deletion mutations, and exposure of said CFTR alleles to detection assays comprising invasive cleavage assays. Broude does not teach simultaneous amplification of at least 20 CFTR alleles and exposure of said alleles to detection assays comprising invasive cleavage assays. As such, Broude does not anticipate the claims and the Applicants request that the Examiner withdraw the rejection.

III. The claims are novel over Shuber

The Examiner has rejected claims 37-38 and 43 under 35 USC §102(b) as allegedly being anticipated by Shuber. In particular, the Examiner contends that Shuber teaches high throughput sequencing of the CFTR gene via amplification methods and exposing the amplified target nucleic acids to at least 20 detection assays (Office Action, pages 4-5). The Applicants respectfully disagree that Shuber anticipates claims 37-38 and 43. However, as previously stated the claims have been amended to recite simultaneous amplification of at least 20 CFTR alleles and exposure of said CFTR alleles to detection assays comprising invasive cleavage assays. Shuber does not teach simultaneous amplification of at least 20 CFTR alleles and exposure to detection assays comprising invasive cleavage assays. As such, Shuber does not anticipate the

claims and the Applicants respectfully request that the Examiner withdraw the rejection.

IV. The claims are not obvious under Hsu in view of CFMDB, Fors and Hall

The Examiner has rejected claims 28-47 under 35 USC §103(a) as allegedly being unpatentable over Hsu et al. in view of the CFMDB, Fors and Hall. In particular, the Examiner contends that Hsu teaches PCR Invader® assays useful in genotyping SNPs, wherein the use of fluorescence polarization allows for multiplexing of SNP detection (Office Action, page 6). Even though Hsu does not specifically teach the amplifying of CFTR alleles, the Examiner contends that this deficit is filled by the CFMDB wherein 1542 CFTR mutations are listed (Office Action, page 6). The Examiner further contends that Fors teaches the benefits associated with Invader technology, and Hall teaches the pitfalls of high cycle number during amplification (Office Action, pages 7-9). The Applicants respectfully disagree with the Examiner's rejection.

As stated above, the claims have been amended to recite "…simultaneously amplifying ….. at least 20 CFTR alleles from said CFTR target nucleic acid wherein said at least 20 CFTR alleles comprise single nucleotide polymorphisms and deletion mutations….to generate said at least 20 amplified CFTR alleles…and exposing said at least 20 amplified CFTR alleles to… detection assays wherein said detection assays comprise invasive cleavage assays …." Hsu teaches SNP amplification of genomic DNA followed by invasive cleavage assays and further followed by product visualization utilizing fluorescent polarization. Hsu does not teach multiplex amplification of at least of 20 CFTR alleles wherein said alleles comprise both SNPs and deletion mutations, and exposure of the CFTR alleles to invasive cleavage assays. Fors teaches SNP scoring using non-amplified DNA, and in fact contrasts and recommends the use of the Invader® system at that time (2000) against using PCR amplified DNA for SNP detection. Fors does not teach simultaneous amplification of at least 20 CFTR alleles, wherein said alleles comprise both SNPs and deletion mutations, and exposure of the amplified CFTR alleles to invasive cleavage assays. Hall teaches amplification of fluorescent signal in an Invader® assay using a FRET based system, where an already generated PCR product is added to the Invader® assay. Hall does not teach multiplex amplification of CFTR alleles (e.g., at least 20 alleles wherein said alleles comprise SNPs and deletion mutations) and exposure of the amplicons to invasive cleavage assays. The CFMDB does nothing more than list known mutations to the

CFTR protein that have been linked with cystic fibrosis; no methods of amplifying and/or detecting such mutations are discussed, nor is any guidance given as to which alleles from the multitude listed might be candidates for multiplexing.

None of the references cited, either alone or in combination, teach or suggest simultaneous amplification of at least 20 CFTR alleles comprising both SNPs and deletion mutations, and exposure of the alleles to a plurality of detection assays comprising invasive cleavage assays. As such, none of the references cited, either alone or in combination, teach or suggest all the claim limitations as required to provide a *prima facie* case of obviousness. Therefore, the Applicants request that the Examiner withdraw the rejection.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 608-218-6900.

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